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Cockatiel-Induced Hypersensitivity Pneumonitis

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Diagnosing an environmental or occupationally related pulmonary disorder often involves a process of elimination. Unlike commonly diagnosed conditions in other specialties, a cause-and-effect relationship may be implied, yet other factors such as temporality and biologic plausibility are lacking. Our patient was referred with a suspected work-related pulmonary disorder. For several years, she had suffered with dyspnea on exertion and repeated flulike illnesses. She worked at an automobile repair garage that performed a large number of emission tests, and there was concern that her workplace exposures were the cause of her symptoms. After a careful review of her history, physical examination, and laboratory testing, we came to the conclusion that she had hypersensitivity pneumonitis related to pet cockatiels in her home. Clinical points of emphasis include the importance of a complete environmental history and careful auscultation of the chest when performing the physical examination. In addition, we encountered an interesting physical diagnostic clue, a respiratory sound that assisted with the eventual diagnosis. **Key words:** bird-breeder's lung, bird breeding, cockatiels, hypersensitivity pneumonitis, inspiratory squawk, lung, precipitin antibodies, respiratory sounds. *Environ Health Perspect* 110:735–738 (2002). [Online 5 June 2002]

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Case Presentation

A 54-year-old female who was employed at an automobile repair garage was evaluated at the University of South Florida (USF) Interdisciplinary Clinic in February 1998. Her primary complaints included dyspnea on exertion and generalized fatigue for several years. She believed her symptoms were work related. She had worked as the automobile parts person at the garage for approximately 3 years. Because of her close proximity to the automobile repair area, she had daily exposure to automobile exhaust and solvent vapors. After the installation of automobile emissions testing equipment in late 1995, she believed that her exposure to auto exhaust increased drastically. To test the emissions, automobiles were required to idle their engines for several minutes. The patient was convinced that the automobile exhaust exposure was responsible for her declining health status.

On detailed questioning, the patient did recall symptoms that pre-dated the installation of the emissions tester. In the year before installation of the emissions tester, she visited her primary care physician monthly because of repeated, flulike illnesses characterized by a cough, persistent fatigue, intermittent hoarseness, dyspnea,

repeated bouts of fever, and night sweats. By the time she was evaluated at the USF clinic, she had been taking prednisone for approximately 6 months. Her initial dose of prednisone was 60 mg/day; however, the dosage was tapered to 10 mg/day as she slowly improved. She continued to note intermittent systemic symptoms, persistent right scapular pain, hoarseness, dyspnea on exertion, a productive cough, and headache.

The patient did not smoke, but she did drink alcohol on a social basis. She raised cockatiels as a hobby. Typically, there were at least six birds in a sunroom in her home. However, she had kept up to 20 birds at one time over the preceding 3 years. Two times a week, she cleaned the bird area and groomed the birds.

At her office visit, she was in no acute distress, and her vital signs were normal. Her breath sounds were of normal intensity on auscultation of her chest. However, at both lung bases, there were bursts of late-inspiratory crackles with the intermittent appearance of a high-pitched, wheezelike sound. The sound was best characterized as a wheeze, whoop, or a cooing-type sound. The late inspiratory musical-type sound appeared concomitantly with, or immediately after, the beginning of the rales.

The chest X ray showed bilateral pulmonary interstitial changes in both lower lung fields. Pulmonary function testing revealed reduced lung volumes, including forced ventilatory capacity (46% of predicted), forced expiratory volume in 1 sec (54% of predicted), total lung capacity (53% of predicted), functional residual capacity (43% of predicted), and carbon monoxide diffusing capacity (36% of predicted). In addition, oxygen saturation fell from 89% to 85% during a standardized exercise study.

Pathologic interpretation of a trans-bronchial biopsy revealed acute and chronic inflammatory interstitial and alveolar processes, with areas of organizational changes in alveolar spaces associated with proteinaceous material. No granulomas were identified. These findings were consistent with bronchiolitis obliterans with organizing pneumonia.

In addition, a number of blood tests were performed. Indicators of nonspecific inflammation and autoimmune activity, such as C-reactive protein, rheumatoid factor, and anti-nuclear antibody titers were within normal limits. Specific IgG and IgM antibody titers for *Chlamydia trachomatis* were negative. Serum measurements for specific IgE to bird allergens were negative for parrot feather and Australian parrot antigen.

The patient's serum was sent for a hypersensitivity antibody panel (Jordan Fink, Medical College of Wisconsin, Milwaukee, WI). We chose to send the sample to an academic laboratory because typical commercial laboratories do not use a standardized panel of bird precipitin antibodies, which may lead to a falsely negative test and a missed diagnosis. Precipitating antibody titers showed a positive reaction to cockatiel droppings extract (DE) and also to pigeon sera. Additionally, there

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were very weakly positive precipitin antibody reactions to pigeon DE, canary DE, and parakeet DE.

After reviewing the clinical history, physical examination findings, chest X ray, and laboratory findings, the patient was diagnosed with cockatiel hypersensitivity pneumonitis. She refused to undergo an open lung biopsy. She was instructed to remove the cockatiels from her home and referred to her private physician for further follow-up.

Discussion

Bird fancier's pulmonary hypersensitivity reactions can be caused by a variety of different birds, but it is most commonly reported for pigeons (1). The Psittaciformes family of birds has more than 300 species of brightly colored, noisy, tropical birds, to which the general name "parrot" is applied (2). Specific species of Psittaciformes include keas, cockatoos, cockatiels, lorries, lorikeets, parrotlets, parakeets, budgerigars, rosellas, conures, lovebirds, mazzons, and macaws. In the mid-1950s, budgerigars (*Melopsittacus undulatus*), or "budgies," became popular household pets in the United States; within a decade, more than 5.5 million people had at least one in their homes (2). Characteristically, the Psittaciformes birds have short necks, tarsi, and wings. In addition, they have a distinctive short bill, which is strongly hooked. The qualities of Psittaciformes birds, especially the ability of many species to imitate human sounds, make them popular as pets. Another appealing attribute of parrots is their display of affection, not only to others of their own species but to humans.

Hypersensitivity pneumonitis (HP) in our patient was caused by pet cockatiels (Figure 1). Although HP caused by other birds has been described, there are few reports dealing specifically with cockatiel HP (4–7). Grammer et al. (7) described four children and five adults with bird fancier's lung. Most patients had exposures to parakeets, parrots, doves, or pigeons. One 6-year-old girl was exposed to both a cockatiel and parakeet and presented with cough, fever, anorexia, and weight loss. In that report (7), all patients had an exposure source in their homes and presented with a chronic form of HP. This is similar to our patient, who presented with a chronic form of the disease after an extensive exposure period.

The specific sources and characteristics of the cockatiel antigen are unknown. Parrots have relatively few feathers, which are hard in texture and normally brightly colored (2). Powder downs, which occur in some parrots, are specialized feathers, usually found in well-defined patches that produce a powdery substance used to clean and waterproof the other feathers. They are well developed in

cockatoos, in which they occur primarily as a pair of lateral rump patches. Skin glands are almost entirely lacking in birds, but there is an oil gland known as the uropygial gland, which is located at the base of the tail. It is also called the preen gland because of its function. The products of the gland are used to clean and waterproof the feathers. Oil is squeezed from the gland, and the birds either use their bills or head to apply it to the feathers.

The first patients with bird fancier's lung reported in the mid-1960s were exposed to pigeon droppings and plumage in the course of raising birds (5,6). Most reports dealing with pigeon breeder's disease used antigens derived from composite pigeon droppings. It is believed that pigeon droppings samples contain antigenic material derived from IgA in pigeon serum, pigeon-excreta material, fragmented feathers, waxing substance coating the feathers, and intestinal mucin (1,7–10). A report on purification of the antigenic component related to pigeon breeder's disease identified a 21-kDa protein in pigeon droppings that showed some similarity to *Saccharomyces cerevisiae* chromosome X reading frame (8).

There is likely antigenic cross-reactivity among bird antigens, especially in the parrot family. In fact, our patient showed definite positive precipitins to cockatiel antigen, as well as a definite positive reaction to pigeon sera and very weakly positive precipitin reactions to droppings extracts of pigeons, canaries, and parakeets. There has been little research characterizing the difference in antigens among bird varieties. Most likely, the cockatiel antigen is small (< 3 µm) and thus can be inhaled into the alveoli and distal bronchioles, where it is cleared by local lymphatic drainage to hilar nodes. This process seems instrumental in inducing an IgG antibody response (11,12). In addition, the cockatiel antigen may possess adjuvant properties that can activate complement by an alternative pathway (11). Theoretically, the antigen stimulates macrophages that interact with a specific receptor. This phenomenon then leads to interleukin (IL)-1 and tumor necrosis factor release that enhances delayed cellular immunologic responses (11,12).

Although it is true that the provoking antigens in HP have certain important characteristics, the patient who develops HP probably has some underlying susceptibility. There is an interaction between host and antigen that seems to be influenced by both genetic and environmental factors (11). The hypersensitivity response in HP is a combined process, consisting of both a type III immunologic reaction (e.g., Gell and Coombs reaction) that produces blood precipitin antibodies, and a type IV lymphocytic reaction

that initiates granulomatous inflammation in the distal bronchioles and alveoli (11).

It is often difficult to differentiate HP from a variety of other types of diffuse lung disorders because there is no single clinical feature or laboratory test that is diagnostic of HP. A diagnosis of HP is often reached after using a combination of clinical, radiographic, and pathologic findings (11). Bourke et al. (11) suggested the following steps in diagnosing HP:

- Identify exposure to a provoking antigen
- Demonstrate an immune response to the antigen
- Establish the relationship of symptoms to antigen exposure
- Assess the degree of impairment of lung function
- Determine the extent of radiographic abnormality
- Consider the need for lung biopsy or bronchoalveolar lavage
- Consider usefulness of a natural or laboratory-based challenge study
- Exclude alternative diagnoses (e.g., sarcoidosis, inhalation fevers)

An important diagnostic clue in our patient was her clinical presentation of diffuse pulmonary findings and constitutional symptoms. A constellation of symptoms such as a repeated flulike illness, intermittent fever, weight loss, and excessive fatigue should lead one to consider HP.

Although HP usually involves the distal gas exchange portion of the lung, there is often an airway component with physiologic



Figure 1. Pied male and hen cockatiel. Photograph reproduced with permission from the American Cockatiel Society (3). Breeder/photographer: Debra Maneke.

evidence of both large and peripheral airway obstruction. In addition, there may be histologic evidence of bronchitis and bronchiolitis (13–15). Our patient did have the pathologic findings of bronchiolitis. An airway component with chronic cough and sputum production is common in pigeon fanciers (14–17). Our patient did report suffering from a long-standing, persistent cough. It is not certain if the bronchial aspect of the HP is truly a specific, immunologically mediated bronchitis or whether it results from a direct inflammatory effect from the inhaled organic dust.

On auscultation of our patient's chest, we heard an unusual inspiratory sound that occurred at the same time or shortly after the beginning of late-inspiratory crackles. We heard a high-pitched inspiratory sound that could be best characterized as a whoop, chirp, or cooing sound. It was difficult to characterize, but it was similar to an inspiratory wheeze. We later learned, upon reviewing the literature, that this auscultatory finding is known as a "squawk" (18–20). Earis et al. (18) was helpful for making the correct diagnosis. These authors were previously aware of a short, isolated inspiratory sound ("squawk") in patients with pulmonary fibrosis due to various causes. During a 1-year period, they discovered the physical finding in 14 patients, of whom 9 were suffering from extrinsic allergic alveolitis. They reported on the clinical and phonopneumographic features of the inspiratory squawk in their 14 patients (18). In 13 of the 14 patients, the high-pitched inspiratory sound was heard over the upper chest, while in one patient (with rheumatoid disease) it was maximal over the lower chest. In 4 patients with extrinsic allergic alveolitis, it was also audible at the mouth. The inspiratory sound was most easily heard with a patient in a semi-recumbent position while breathing deeply. Very deep breathing, coughing, and exercise, however, often abolished the sound, in some patients for several minutes. The squawk was intermittent, particularly in patients with extrinsic allergic alveolitis, where it sometimes occurred only once or twice a minute. Despite this breath-to-breath variation, the sign was remarkably constant from one clinic visit to the next. In one patient with extrinsic allergic alveolitis, it

was present for 4 years. In extrinsic allergic alveolitis, the squawk was of higher frequency and shorter duration and occurred later in inspiration than in the other groups of diffuse pulmonary fibrosis. In all patients, the squawk was preceded by inspiratory crackles. Figure 2 shows an example of a phonopneumograph of a typical squawk heard in extrinsic allergic alveolitis. It was postulated that the squawk was likely generated by air rushing into small airways, causing the walls and surrounding tissue to oscillate. The late inspiratory crackles are believed to arise from smaller and more peripheral airways that open late in inspiration. High frequency sounds are known to require a smaller vibrating mass of tissue than sounds of lower pitch. The squawk probably occurs later in inspiration with extrinsic allergic alveolitis because small peripheral airways are affected.

Once HP was a consideration, it was important to document that there was an exposure to a provoking antigen capable of causing HP. In our patient, the provoking agent was cockatiel antigen. She frequently handled her birds and cleaned the cages; thus she was exposed to a number of potential antigens. In the literature, there is little specific information on cockatiels, but studies with pigeon fancier's HP suggest that the occurrence of the disease is partly related to the intensity and perhaps the duration of contact with pigeon antigens (1,11,12). When considering patients with suspected Psittaciformes HP, important environmental risk factors to consider are antigen concentration, duration of exposure, frequency of exposure, particle size, antigen solubility, genetic factors, and cigarette smoking status (1,11).

It is important to emphasize that HP is not a uniform disease entity. Rather, it is a complex and dynamic clinical syndrome that varies in its initial presentation and clinical course. Over time, different patterns of disease may emerge. The interaction of antigen exposure and host response in the initiation and progression of HP is considerably complex, and the clinical course is unpredictable (11,12). Classically, bird breeder's lung has been divided into three stages: acute, subacute, and chronic (21). Even with continued exposure, a patient may not progress from the acute stage to the chronic stage. Conversely, persons may skip the acute and subacute stages altogether. Recently, Bourke et al. (11) have adopted a clinical classification of HP that emphasizes the dynamic nature of the disease and allows for the evolution of different clinical patterns over time: acute progressive, acute intermittent nonprogressive, and recurrent nonacute. In the recurrent, nonacute disease, the symptoms are chronic and nonspecific in nature and therefore may lack an apparent temporal

relationship to antigen exposure. This may be the case for our patient. In this form of the disease, the patient presents with chronic respiratory complaints, impaired lung function, and evidence of pulmonary fibrosis and emphysema.

The factors that determine the initial clinical presentation and subsequent course of HP are likely to involve both the circumstances of antigen exposure and a range of modulating factors governing the immune response in an individual. For example, in an early report of pigeon fancier's lung disease, a patient continued to keep pigeons without experiencing exacerbations (21). Long-term follow-up studies showed that some bird fanciers had normal pulmonary function despite suffering acute, intermittent, nonprogressive HP for many years (17). In Mexico, pigeon fancier's lung usually occurs in females who keep domestic pigeons in their homes (12,16). In this environment, antigen exposure is prolonged and of a low-grade nature. The disease usually pursues an insidious clinical course without acute episodes. Often, the disease resembles other chronic interstitial lung diseases such as idiopathic pulmonary fibrosis.

The positive identification of an immune response to an antigen of interest is helpful in establishing the diagnosis of hypersensitivity pneumonitis. In our patient, we did this by demonstrating positive serum precipitin to cockatiel antigens. It is important to emphasize that the finding of such an immune response only confirms that the patient had a sufficient level of exposure to the antigen to develop sensitization or immunologic responsiveness. This finding alone is not sufficient to establish a definitive diagnosis of HP (12,16). The reason for this qualification is that many asymptomatic subjects without HP show similar levels of humoral or cellular responses similar to symptomatic patients suffering from active HP (12,16). In many instances, there is a level of cross-reactivity between different bird antigens. The cross-reactivity responses do not necessarily represent an immunologic reaction to all of the different bird antigens (22). We saw weak precipitating antibody reactions to other bird antigens besides cockatiel, even though there was not repeated exposure to the other birds.

Other diagnostic criteria for HP include findings of restrictive lung disease with reduced lung volumes in typical pulmonary function tests (17). There is reduced carbon monoxide diffusing capacity. Our patient demonstrated exercise hypoxemia, which is a sensitive physiologic indicator of diffuse interstitial lung disease. In addition, her chest X ray was consistent with HP. The chest X ray may show an alveolar process,

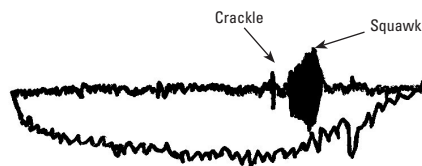


Figure 2. Phonopneumograph with simultaneous inspiratory tracing demonstrating a late inspiratory crackle followed by a squawk. Adapted from Earis et al. (18).

reticulonodular pattern, and evidence of fibrosis. Although a computerized tomography (CT) scan was not available for our review, a CT is more sensitive than a standard X ray, and we would have expected a characteristic ground-glass pattern. Diffuse bilateral patchy or ground-glass opacifications are noted in 50–70% of patients with HP (23). Other CT findings in HP include areas of decreased attenuation, air trapping, poorly defined nodules, and honeycomb lung (23,24).

In our evaluation, we considered other types of interstitial lung disease. Our patient had a transbronchial biopsy consistent with bronchiolitis obliterans with organizing pneumonia. We did not have access to an open lung biopsy, which is preferable and provides more lung tissue for examination. Typically, patients with HP show chronic inflammatory infiltration along small airways, diffuse interstitial inflammation mainly of lymphocytes, and scattered, small, non-necrotizing granulomas (14,25). Perez-Padilla et al. (15) described bronchiolitis in chronic pigeon breeder's disease. Open lung biopsy of 36 patients with chronic pigeon breeder's disease revealed significant peribronchiolar inflammation. The microscopic bronchiolar changes in chronic pigeon breeder's disease appeared different from those described for farmer's lung (15). Generally, transbronchial biopsy is not sufficient for proper pathologic examination of lung tissue; however, the limited pathologic

findings in our patient do corroborate the clinical picture (25). Initially, we considered usual interstitial pneumonia, but we determined that the clinical findings are most consistent with HP.

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